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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,581	04/20/2006	Hitoshi Ban	0020-5482PUS1	2390

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
06/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/576,581	BAN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6-18,20,24,27 and 29-35* is/are pending in the application.

4a) Of the above claim(s) *6-9,14,15,17,18,27,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,10-13,16,20,24,29-32 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/30/2009* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :5/15/2009;07/21/2006; 04/20/2006.

DETAILED ACTION

1. This application is a 371 of PCT/JP04/15773 filed 10/19/2004 and claims priority to JAPAN 2003-361256 filed 10/21/2003.

Claims 3-4, 6-18, 20, 24, 27, 29-35 are pending. Claims 27, 33-34 are withdrawn.

Previous Restriction Requirement Withdrawn

2. The previous restriction requirement as set forth in the action dated January 13, 2009 is hereby withdrawn. The examiner had restricted on the variable Z and p rather than the Y' variable. This was inadvertent since previous to the claim amendment of April 15, 2009, the Y' variable and Z variable had substantial overlap where p was equal to 0. The elected species falls under group V, as can be clearly seen in the examiners structural drawing in the Figure 1 sent out with the previous restriction. The examiner called the applicant's representative Mr. Nuell on April 30, 2009 to clarify and revise the restriction requirement over the phone, (See attached interview summary of 4/20/2009). A new restriction requirement is set forth below.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, R^1 is aryl (i.e. aromatic hydrocarbons), Y' is aryl (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1,4-diaryl piperidines, shown as structure **I** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group II, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, R^1 is aryl, Y' is heteroaryl (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-aryl-4-heteroaryl-piperidines, shown as structure **II** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group III, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, Y' is aryl (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), R^1 is a heteroaryl, with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-heteroaryl-4-aryl-piperidines, shown as structure **III** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group IV, Claims 1-26 drawn to compounds and compositions reading on X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and R^{19} and R^{20} form piperazine, m is 2, n is 2, Y' aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-piperazinyl-4-aryl-cyclohexanes, shown as structure **IV** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group V, Claims 1-26 drawn to compounds and compositions reading on X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} do not form a ring, m is 2, n is 2, Y' aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-amino-4-aryl-cyclohexanes, shown as structure **V** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group VI, Claims 1-26 drawn to compounds and compositions reading on X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} form a piperidine ring, m is 2, n is 2, Y' is aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-piperidinyl-4-aryl-cyclohexanes, shown as structure **VI** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group VII, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, R^1 is aryl, Y' is a -COR8a, or alkyl-aryl where R8a is aryl (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), drawn to 1-aralkyl-4-aryl-piperidines, with the proviso that none of the substituents on the X ring form bridges or double bonds, shown as structure **VII** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group VIII, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, Y' is a aryl, R^1 is a aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), where on the X ring the carbons adjacent to the nitrogen form a bridging ethyl group, drawn to diaryl-tropanes, shown as structure **VIII** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group IX, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, Y' is aryl, R^1 is a aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), where on the X ring the carbons adjacent to the nitrogen form a bridging propyl group, drawn to diaryl-azabicyclononanes, shown as structure **IX** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group X, Claims 1-26 drawn to compounds and compositions reading on X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and R^{19} and R^{20} form morpholine, m is 2, n is 2, Y' is aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-morpholinyl-4-aryl-cyclohexanes, shown as structure **X** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XI, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, Y' aryl, R^1 is a aralkyl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), where on the X ring the carbons adjacent to the nitrogen form a bridging ethyl group, drawn to N-aralkylaryl-tropanes, shown as structure **XI** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XII, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 3, n is 2,, R^1 is aryl, Y' is aryl (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1,4-diaryl azepines, shown as structure **XII** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XIII, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, Z is NR^9R^{10}, where R^9 and R^{10} form piperidine, and Y' is aryl (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-piperidinyl-4-aryl-piperidines, shown as structure **XIII** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XIV, Claims 1-26 drawn to compounds and compositions reading on X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} do not form a ring, m is 3, n is 2, Y' is aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-amino-4-aryl-cycloheptanes, shown as structure **XIV** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XV, Claims 1-26 drawn to compounds and compositions reading on X is N, m is 2, n is 2, R^1 is a arylsulfonamide, Y' is a aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-arylsulfonamide-4-aryl-piperidines, shown as structure **XV** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

Group XVI, Claims 1-26 drawn to compounds and compositions reading on compounds other than those of groups I-XV. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election will be made.

Group XVII, Claim 27, drawn to methods of treating diseases, , limited in scope to one of the compounds of groups I-XVI. If this group is elected, a single disclosed disease and a single disclosed species useful in treating diseases, is also required. Further restriction based on the election may be made.

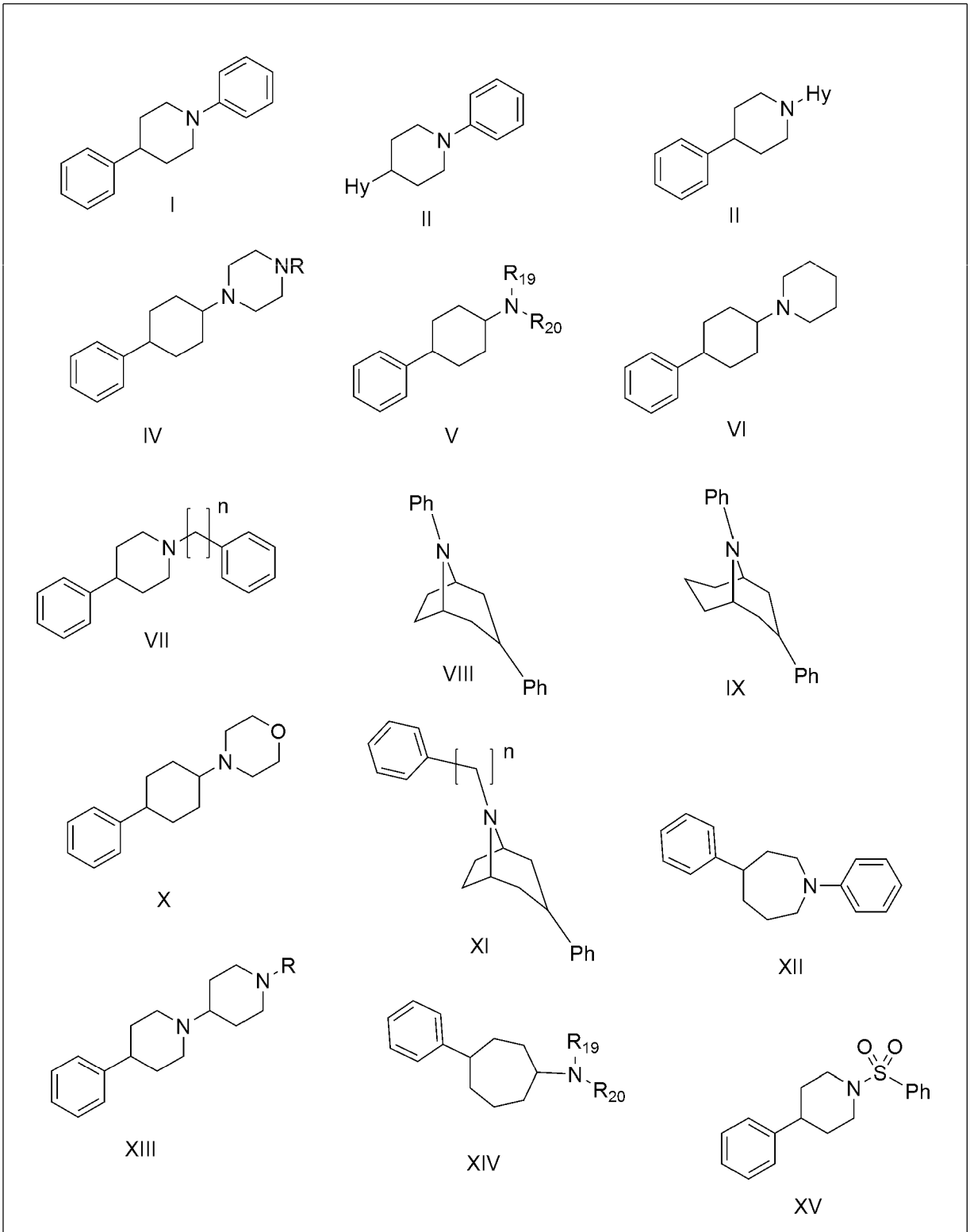


Figure 1. Groups I - XV.

PLEASE NOTE: Claim 28 is a non-statutory use claim and is withdrawn from consideration. Cancellation is recommended.

The inventions listed as Groups I-XVII do not relate to a single general inventive concept under 35 USC 121 or PCT Rule 13.1 because:

PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

PCT Rule 13.2 states that the unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Annex B, **Part 1(a)**, indicates that the application should relate to only one invention, of if there is more than one invention, inclusion is permitted if they are so slinked to form a single general inventive concept.

Annex B **Part 1(b)**, indicates that "special technical features" means those technical features that as a whole define a contribution over the prior art.

Annex B **Part 1(c)**, further defines independent and dependent claims. Unity of invention only is concerned in relation to independent claims. Dependent claims are defined as a claim that contains all the features of another claim and is in the same category as the other claim. The category of a claim refers to the classification of claims according to subject matter e.g. product, process, use, apparatus, means, etc.

Annex B **Part 1(e)**, indicates that the permissible combinations of different categories of claims. **Part 1(e)I**, states that inclusion of an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product is permissible.

Annex B, **Part 1(f)**, indicates the "Markush practice" of alternatives in a single claim. **Part 1(f)I**, indicates the technical relationship and the same or corresponding special technical feature is considered to be met when (A) all alternatives have a common property or activity, and (B) a common structure is present or all alternatives belong to a recognized class of chemical compounds. Further defining (B), Annex B, **Part 1(f)(i-iii)**, the common structure must; a) occupy a large portion of their structure, or b) the common structure constitutes a structurally distinctive portion, or c) where the structures are equivalent and therefore a recognized class of chemical compounds, each member could be substituted for one another with the same intended result. That is, with a common or equivalent structure, there is an expectation relationship and the corresponding special technical feature result from a common (or equivalent) structure that is responsible for the common activity (or property). **Part 1(f) iv**, indicates that when all alternatives of a Markush grouping can be differently classified, it shall no, take alone, be considered justification for finding a lack of unity. **Part 1(f)v**, indicates that
"When dealing with alternatives, if it can be shown that at least *one* Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner"

In the instant case, the majority of the Markush alternatives are not novel because countless prior art references, such as the 31 documents cited in the international search report as

anticipatory X references, describe the compounds of the instant claims, thus the lack of a special technical feature is apparent.
Inventions I-XVI and XVII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case at least the method of treating atherosclerosis can be practiced with diet and exercise.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is *presented prior to* final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be **allowable**, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai; In re Brouwer and 35 U.S.C.§ 103(b)," 1184 O.G. 86 (March 26, 1996).

Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include all the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01. Filing of appropriate terminal disclaimer in anticipation of a rejoinder may speed prosecution and the process of rejoinder.

3. In addition to the selection of an elected group applicant is required to elect a species. All claims are generic to the following disclosed patentably distinct species: the compounds of the specification. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species,** including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Response to Restriction Requirement

4. Applicant's election of group V and the species (the compound "Example 136 (cis-4-[(biphenyl-4-ylmethyl)amino]-l-(3-methoxyphenyl)cyclohexanecarboxyamide shown at page 271 of the English translation of the"), in the telephone conversations of April 30, 2009, May 7, 2009 and the reply filed on May 21, 2009 is acknowledged. The elected species reads on claims 3-4, 10, 11, 12, 13, 16, 20, 24, 29-32, and 35 (i.e. where R^1 is H, X is CR^{15}, R^{15} is $NR^{19}R^{20}$, R^{19}/R^{20} is H or benzyl substituted in the 4-position with a phenyl, Y' is phenyl substituted with methoxy in the 3-position, p is 0, and Z is carbamoyl, R^2-R^5 are H, m is 2 and n is 2). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP §818.03(a)). This requirement is made FINAL. This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination:

Group V, Claims 3-4, 6-18, 20, 24, 29-32, 35 drawn to compounds and compositions reading on X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} do not form a ring, m is 2, n is 2, Y' aryl, (or where p and Z together have the same value as Y' if the claims are amended to exclude Y' as aryl), with the proviso that none of the substituents on the X ring form bridges or double bonds, drawn to 1-amino-4-aryl-cyclohexanes, shown as structure **V** in Figure 1. If this group is elected, a further election of a single disclosed species is also required. Further restriction based on the election may be made.

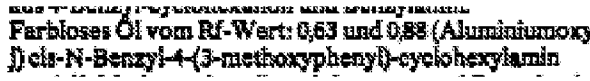
The elected species reads on claims 3-4, 10-13, 16, 20, 24, 29-32, and 35. There is no allowable generic or linking claim, and as such claims 6-9, 14-15, and 17-18 are withdrawn from consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

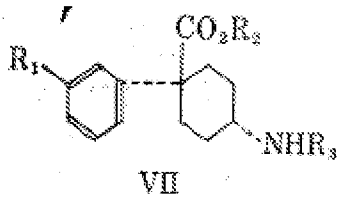
5. Claims 3-4, 10-13, 16, 20, 24, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Maier et. al. DE 4438055 (abstract in English). Maier teaches numerous compounds of the instant claims, where R^1 is H, Z is H, X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} is H or benzyl, and Y' is phenyl substituted with alkoxy, p is 0, R^2-R^5 are H, m is 2 and n is 2 in the cis or trans configuration, such as the compound on page 10 line 56, shown below:



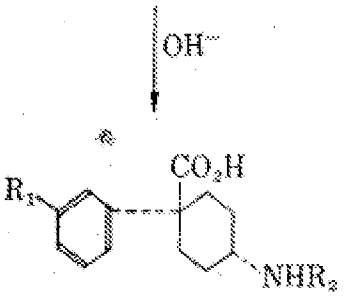
Compositions are also described.

6. Claims 3-4, 10-13, 16, 20, 24, and 35 rejected under 35 U.S.C. 102(b) as being anticipated by Takeda, Mikio et. al. "4-Phenyl-2-azabicyclo[2,2,2]octanes." *Chemical & Pharmaceutical Bulletin*, 1977, 25(4), 775-83.

Takeda teaches numerous compounds of the instant claims, where Z is CO_2R, X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} is $NR^{19}R^{20}$, and where R^{19} and R^{20} is H or alkyl, and Y' is phenyl substituted with alkoxy, in the cis or trans configuration, such as the compounds on page 776, shown below:



VII



IXa : $R_1=R_2=H$
IXb : $R_1=OMe$, $R_2=H$
IXc : $R_1=OMe$, $R_2=Me$

Compositions are also described.

7. Claims 3-4, 10-13, 16, 20, 24, and 35 rejected under 35 U.S.C. 102(b) as being anticipated by WO 2001081295, entire document. Numerous compounds of the instant claims, where R^1 is H, Z is H, X is CR^{15}, R^{15} is $NR^{19}R^{20}$, and where R^{19} and R^{20} is H or benzyl or other aralkyl, and Y' is phenyl substituted with alkoxy and others, p is 0, R^2-R^5 are H, m is 2 and n is 2 in the cis or trans configuration. See tables at page 59ff.

PLEASE NOTE: There are countless documents prejudicial to the patentability of claims 3-4, 10-13, 16, 20, 24, and 35 on the grounds of anticipation.

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3-4, 10-13, 16, 20, 24, 29-32, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. The term "substituted" is indefinite. Unless one knows what a substituent is a determination of what these compounds are cannot be made. The specification does not fully elaborate the identity of these substituents. This rejection is not being made for breadth, which will be discussed at length in this action at 8. A claim is improper when it unnecessarily relies on the specification for a key feature that should be present in the claims, See *Ex Parte Fressola* 27 USPQ2d 1608. The claims should be self-contained; that is, they should not expressly rely upon the description or drawing to give them meaning. A claim which refers to the specification defeats the purpose of a claim.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 30-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The new definition of Y' as "alkoxyphenyl" is a new descriptor and describes a new genus that does not find support in the specification as filed. It may be that the definition in claim 20 was intended, where the phenyl is attached as a substituent, however currently the "alkoxyphenyl" could encompass material where the attachment position is on the alkylgroup. It is suggested that the description in claim 20 be used.

10. Claims 3-4, 10-13, 16, 20, 24, 29-31, and 35. are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows:

$R^1 - R^7$, and R^{19} should be H, Z should be H, CO_2R, carbamoyl, CN, and Y' should have alkoxy or hydroxy groups only.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

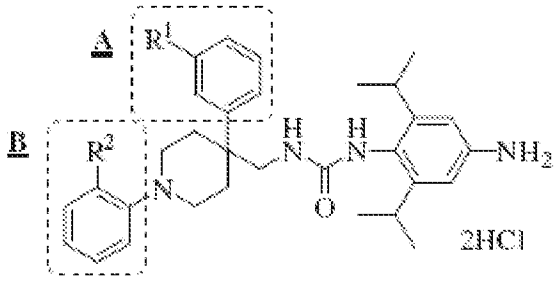
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all heterocycles, carbocycles and other groups bearing multiple substitutions of an unascertainable scope. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as LDL receptor expression enhancer. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal

chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:**

The medicinal chemistry of LDL receptor ligands is relatively well-developed and many limitations are well known in the art. It is sensitive to structural changes that may be relatively minor in the chemical sense see Shigehiro Asano "Synthesis and structure–activity relationships of N-(4-amino-2,6-diisopropylphenyl)- N'-(1,4-diarylpiperidine-4-yl)methylureas as anti-hyperlipidemic agents" Bioorganic and Medicinal Chemistry (2009), doi:10.1016/j.bmc.2009.04.059 in press, pgs. 1-11, whole document. Compare compound **37** or **42** to the other compounds in Table 3, which differ only in the lack of alkylhydroxy group yet they are devoid of activity.

Table 3
Effects of substitution of the alkoxy group at the phenyl moiety (A or B-part) with a hydrophilic group on compounds biological activity towards ACAT and LDL-R and solubility



Compds	R^1	R^2	ACAT[a] IC_{50} (nM))	LDL-R^b@10^{-7} M	Solubility (mg/ml)@ pH 7.4
39	OMe	O^{n}Bu	32	++	0.0003
37	OMe	OH	246	–	Nt[d]
40[c]	OMe	$O(CH_2)_3NH_2$	195	++	0.032
41[c]	OMe	$O(CH_2)_3NMe_2$	239	Nt[d]	>0.25
42	OMe	$O(CH_2)_2OH$	96	++	Nt[d]
43	OMe	$O(CH_2)_3OH$	18	++	0.022
44	OH	OMe	797	–	Nt[d]
45	$O(CH_2)_3OH$	OMe	62	+	Nt[d]
SMP-797			31	++	0.010

[a] Inhibitory activity for ACAT in rat macrophages.
[b] Effect on LDL-R expression in $HepG_2$.
[c] 3HCl salts.
[d] Nt: not tested.

The authors came to the following conclusion "From these findings **we concluded that lipophilicity and/or substituent size are important for good LDL-R up-regulatory activity.**" pg. 4.

See also Asano et. al. "Novel 1,4-diarylpiperidine-4-methylureas as anti-hyperlipidemic agents: Dual effectors on acyl-CoA:cholesterol O-acyltransferase and low-density lipoprotein receptor expression" *Bioorganic & Medicinal Chemistry Letters* **2009** *19*, 1062–1065, who come to following conclusion:

"Compounds 1, 11b–e, and 12a–e inhibitory activity for ACAT and up-regulation of LDL receptor expression are shown in Table 1. As compared to 1 or 11e, the inhibitory activity of 11b, 11c, or 11d for ACAT decreased more than 10-fold. **These findings suggest that the aryl substituent on the nitrogen of the piperidine (A-part) is important for ACAT inhibition. Compounds 1, 11e, and 12a–e inhibited ACAT with similar IC50 values, however, only 12c up-regulated LDL receptor expression. From these results it is assumed that the 2-methoxyphenyl group in A-part (Fig. 1) and the 4-amino-2,6-diisopropylphenyl group in C-part are essential for the dual inhibition of ACAT and up-regulation of LDL receptor expression.** Next, we turned our attention to the effects of a substitution on the phenyl ring of B-part (Fig. 1). The inhibitory activity for ACAT of compounds 12c and 12i–m and their up-regulation of LDL receptor expression are summarized in Table 2. Substitution on the phenyl ring of B-part was well tolerated for ACAT inhibitory activity. **However, for up-regulation of LDL receptor expression, electron donating groups, such as a methoxy group, were preferred to electron withdrawing groups.** Finally, in order to improve both the inhibitory activity for ACAT and the up-regulatory effect on LDL receptor expression, we carried out SAR studies on the 2-alkoxy groups of A-part. As shown in Table 3, 2-alkoxyl substituents on the phenyl ring were well tolerated with IC50 values for inhibition of ACAT ranging from 32 to 68 nM. Interestingly, the up-regulatory effect on LDL receptor expression was improved in the case of n-butoxy (12f)12 and fluoroalkoxy (12g and 12h) as compared to that of compound 12c. **These findings indicate that an increase in compounds hydrophobicity is effective in improving both the inhibitory activity for ACAT and the up-regulatory effect on LDL receptor expression.** Particularly, compound 12f demonstrated biological properties comparable to those of SMP-797." Emphasis added.

Clearly the art shows the high degree of unpredictability and teaches away from making the modifications described by the instant claims. The instant specification gives very little information in regard to the molecular determinants of receptor affinity for the compounds of the instant case. The only information contained in the 288 page specification is found on page 287 and is listed as Table 10:

Table 10

Example Compound	(Concentration)	Activity of LDL receptor(%)
1-4	(10 μM)	134
6-3	(10 μM)	127
7-3	(3 μM)	125
12	(10 μM)	134
20	(10 μM)	123
43-2	(10 μM)	116
44	(3 μM)	135
49-f	(10 μM)	135
55-1	(1 μM)	141
58-1	(10 μM)	152
82	(10 μM)	125
85	(10 μM)	149
89	(10 μM)	195
94	(10 μM)	136
105	(10 μM)	139

It is unclear which if any of these compounds actually read on the elected invention, at least the elected species has not been shown to have any biological activity. Regardless, these compounds bear a remarkable structural resemblance to one another, yet the claims are not commensurate in scope. The only real structural variation that is present is in the R^{20} variable. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

It is very clear that one could not make/use this very broad invention that has only a few working examples in this unpredictable art without undue experimentation.

11. Claim 3-4, 10-13, 16, 20, 24, 29-32, and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found on pages 34-35, which basically just states what a prodrug might be. c) There is no working example of a prodrug of a compound the formula I. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the billions of compounds of formula of claim 3 as well as the presently unknown list of potential prodrug derivatives embraced by claim 3.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular unknown dervative is, in fact, a prodrug.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/

Primary Examiner, Art Unit 1625